

REMARKS

Claims 42-62 are pending in this application. By amendment above, claims 42-44 have been amended to cancel reference to non-elected embodiments of the invention, and claims 59-61 have been canceled. Claim 62 has been amended to place it in independent form and to cancel reference to several specific diseases or conditions. Applicants specifically reserve the right to file one or more divisional applications directed to non-elected subject matter of this application.

Claims 59-62 have been rejected under 35 U.S.C. § 112, first paragraph, on the basis that although the claims are enabled for the administration of the claimed compounds to treat pain, the specification does not enable the administration of the compounds for treating or preventing diseases mediated by cyclooxygenase-2. This rejection is traversed.

By amendment above, Applicants have canceled claims 59-61 and amended claim 62 to place it in independent form and to cancel several specific diseases and conditions listed therein. The claim now focuses on a method of treating inflammation, particular cancers and pain mediated by COX-2. The examiner has acknowledged that Applicants have enabled the treatment of inflammation. Applicants also wish to point out to the examiner

that test 3 on pages 29-30 of the application is directed to the treatment of pain. Accordingly, Applicants respectfully submit that they also have enabled methods of treating pain mediated by COX-2. In addition, Applicants enclose herewith as Attachment A a copy of Koki, A. and J. Masferrer, *Cancer Control*, 9 (No.2 supplement):28-35 (2002), a paper which provides an overview of the evidence that COX-2 inhibitors are useful in the treatment and prevention of cancer. The entire paper focuses on the relationship between COX-2 and cancer and on evidence that COX-2 inhibitors may prevent or treat cancer. The examiner's attention is directed, for example, to the following statements:

In general, COX-2 is expressed in 40% to 80% of neoplastic cells in human cancers and the extent and intensity of expression is greater in cancerous than in noncancer cells. Moreover, well- and moderately-differentiated cancers have significantly higher COX-2 expression than poorly differentiated cancers. COX-2 is also detected in non-cancerous cells (<2 mm) and in the angiogenic vasculature within tumors and in pre-existing blood vessels adjacent to tumors. In contrast, COX-2 is not detected in the vasculature of normal tissues.

(page 30, second column, footnote omitted)

COX-2 is overexpressed along the continuum of oncogenesis and is likely to be a key player in a number of biologic pathways leading to cancer. Current evidence indicates that COX-2 promotes tumor-specific angiogenesis, inhibits apoptosis, and induces proangiogenic factors such as VEGF, inducible nitrogen oxide synthase promoter (iNOS), IL-6, IL-8, and TIE-2.

(page 31, second column, footnotes omitted)

COX-2 inhibitors have been shown to markedly inhibit tumor growth and metastasis in several animal models of colon, skin, lung, bladder and breast cancers."

(page 32, first column, footnotes omitted)

We have presented data to support the hypothesis that COX-2 activity modulates critical steps in the initiation, promotion, and progression of several human epithelial cancers.

...

In summary, COX-2 is overexpressed in both early and late stages of carcinogenesis and has been shown to be efficacious as monotherapy and in combination with conventional chemotherapeutics in relevant animal models. Taken together, the epidemiological data and preclinical studies in animal models have generated compelling interest in the potential use of COX-2 inhibitors in chemoprevention and chemotherapy of human tumors.

(page 33, columns 1 and 2).

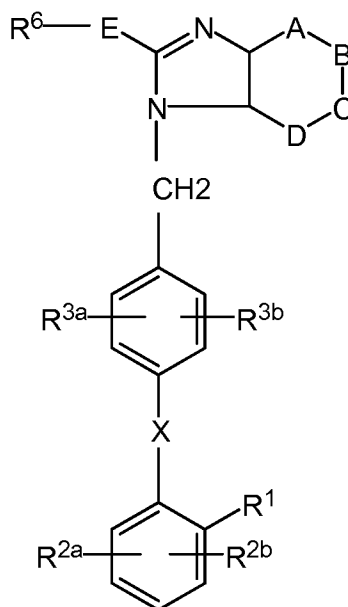
Applicants also enclose herewith as Attachment B a copy of Turini, M. and R. DuBois, *Ann. Rev. Med.* 53:35-57 (2002), which further discusses the role of COX-2 inhibitors in treating the diseases listed in claim 62.

Applicants respectfully submit that in view of the foregoing, claim 62 as amended is enabled.

Claims 42-62 have been rejected under 35 U.S.C. § 102(b) as anticipated by Chakravarty et al., CAS 120:45975. The examiner asserted that the reference discloses a compound 150589-21-2, which anticipates the compounds of formula (i) when the variable R1 is phenyl-alkyl, the variable D is phenyl, the variable A is an unsaturated 6-membered ring (i.e., phenyl), the variable L is

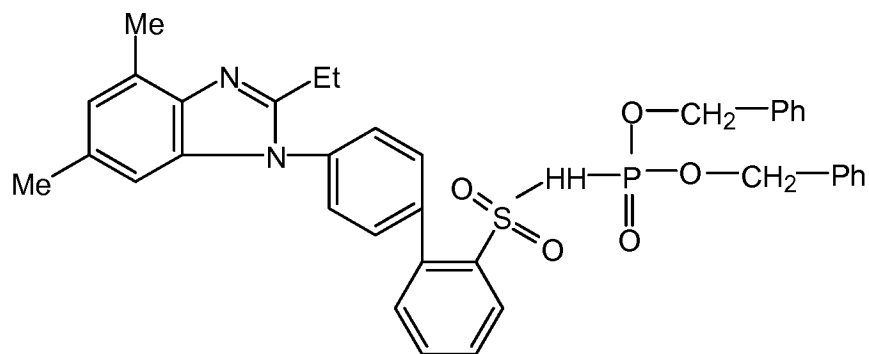
a bond and the variable B is a substituted heteroaryl. This rejection is traversed.

The generic structural formula given in CAS RN 150589-21-2 is as follows:



I

The reference also gives the structure of a specific compound, identified as phosphoric acid, [[4'-(2-ethyl-4,6-dimethyl -1H-benzimidazol-1-yl)[1,1'-biphenyl]-2-yl]sulfonyl]-, bis(phenylmethyl) ester, designated as compound 150589-21-2, which is depicted as



As an initial point, Applicants wish to note that this latter structural formula is incorrect; the generic structure includes a -CH<sub>2</sub>- group, in between the phenyl group with the R<sup>3a</sup> and R<sup>3b</sup> substituents and the benzimidazole ring system, which is missing in the depiction of formula II. The -CH<sub>2</sub>- group is, in fact, a necessary part of the structural formula; formula I of CAS 120:45975 originates in GB patent application no. GB 2262637, a copy of which is attached hereto as Attachment C. Looking at the examples of the '637 application, it can be seen that table I of the examples on page 28 relates to benzimidazoles, such as that of formula II above (see, specifically, line 13 of page 29 for the specific compound set forth as formula II), but the -CH<sub>2</sub>- between the heterocyclic group and the phenyl group is always present. Similarly, the examples listed in table II of the '637 application, on page 30, relate to imidazopyridines with the -CH<sub>2</sub>- moiety present between the heterocycle and the phenyl ring.

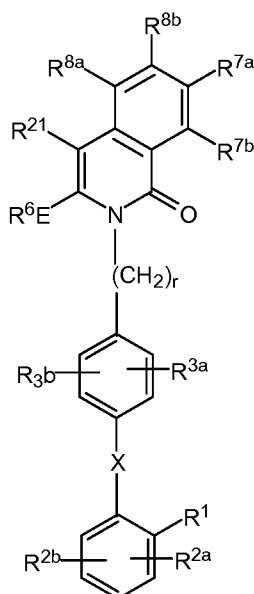
Specific examples of compounds of the invention are set forth beginning on page 37 of the '637 application; all the compounds have the -CH<sub>2</sub>- bridge between the heterocyclic group and the phenyl group.

Thus, as noted above, there is an error in the depiction of compound 1505589-21-2 of the cited reference. The compounds of the present invention do not include a -CH<sub>2</sub>- bridge between the heterocyclic ring system and ring A. The bridge in the compounds of claim 42 is designated by the variable L, which is defined as being selected from a bond, -O-, -S- or -NR<sup>3</sup>-. On this basis alone, the reference does not anticipate the compounds of claim 42.

There are, however, further differences between the compounds of formula I of the reference and the presently claimed compounds. Notably, as restricted by the examiner, ring A of the compounds of claim 42 is a five-membered heterocyclic ring, not a phenyl group as in the reference. In addition, claim 42 provides that the substituents L and D are placed on adjacent atoms of ring A, whereas the corresponding substituents of the reference are on the 1 and 4 carbon atoms of the central phenyl group. For all of these reasons, the presently claimed compounds are novel over the compounds of CAS 120:45975.

For all of the reasons set forth above, Applicants respectfully submit that the cited reference does not anticipate the claims of the present application.

Claims 42-62 also have been rejected under 35 U.S.C. § 103(a) as unpatentable over Chakravarty et al., U.S. Patent 5,162,340. The examiner noted that the patent discloses compounds of the formula:



and that the variable R<sub>1</sub> can represent -SO<sub>2</sub>NH-P(O)(R<sup>24</sup>)<sub>2</sub>- and R<sup>24</sup> can represent alkoxy. The examiner asserted that the difference between the present claims and the reference is that in the present claims the variable A represents an unsaturated 6-member ring (i.e., phenyl) or imidazole, whereas in the reference there is an unsaturated 6-member (i.e., phenyl) at the same position.

He asserted that the compounds of the '340 patent inherently overlap with the compounds of the present invention. He stated that one of ordinary skill would have been motivated to employ the compounds of the '340 patent to obtain the compounds of present formula I, wherein the variable D represents phenyl, the variable A represents an unsaturated 6-member ring (i.e., phenyl), the variable L is a bond, and the variable B represents substituted heteroaryl. This rejection is traversed.

In the formula of the '340 patent, the portion of the formula corresponding to D of the present formula I is a phenyl group, X can be a bond and the portion of the compound corresponding to A of the present formula I is a phenyl group. The portion of the formula corresponding to L of the present formula I is a methyl or ethyl group (r is defined as 1 or 2).

As noted above, the examiner has asserted that variable A in the presently claimed formula I is an unsaturated 6-member ring or imidazole, that the corresponding variable in the formula of the '340 patent is a phenyl ring, and that one would use that similarity, in part, to obtain the compounds of the present invention. Applicants note, however, that as a result of the restriction requirement, variable A in the present formula I has been restricted to certain unsaturated 5-member heterocyclic rings: imidazole, pyrazole, isoxazole or oxazole.



As the formula of the reference includes a phenyl ring (with no other options) at a position corresponding to an unsaturated, heterocyclic, five-membered ring of the presently claimed formula, there is no "inherent overlap" between the two formulas as the examiner had asserted. Furthermore, there is nothing in the reference to suggest replacing the phenyl ring with an unsaturated, heterocyclic five-membered ring.

In addition, there are further distinctions between the formula of the '340 patent and the present formula I. Variable L in the presently claimed formula I is a bond, -O-, -S- or  $\text{NR}^3$ -; the comparable portion of the '340 formula is a methyl or ethyl group  $(-\text{CH}_2)_r$ , wherein r is defined as 1 or 2). In addition, variable B of the present formula I does not encompass the fused heterocyclic rings of the '340 formula; B can be a substituted heteraryl group which the ring can be substituted with one or more substituents  $\text{R}^4$ , but the  $\text{R}^4$  substituents are either individual elements or small groups or two  $\text{R}^4$  substituents on the same carbon atom can be taken together to form an oxo group or one  $\text{R}^4$  substituent can be a 5- or 6-membered ring which in turn can be substituted.

In view of all of these differences, the examiner's assertion that one would be motivated to make the claimed compounds in view of the compounds of the '340 patent because

they "would possess similar activity (i.e. composition)" is not tenable. There are significant differences between the structural formula of the '340 patent and that of the present formula I. Furthermore, although the examiner made reference to "similar activity," he provides no support for this conclusion and, in fact, the activity of the claimed compounds is quite different from that of the compounds of the '340 patent.

In view of the foregoing amendments and discussion, Applicants respectfully submit that the pending claims of this application are in condition for allowance.

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